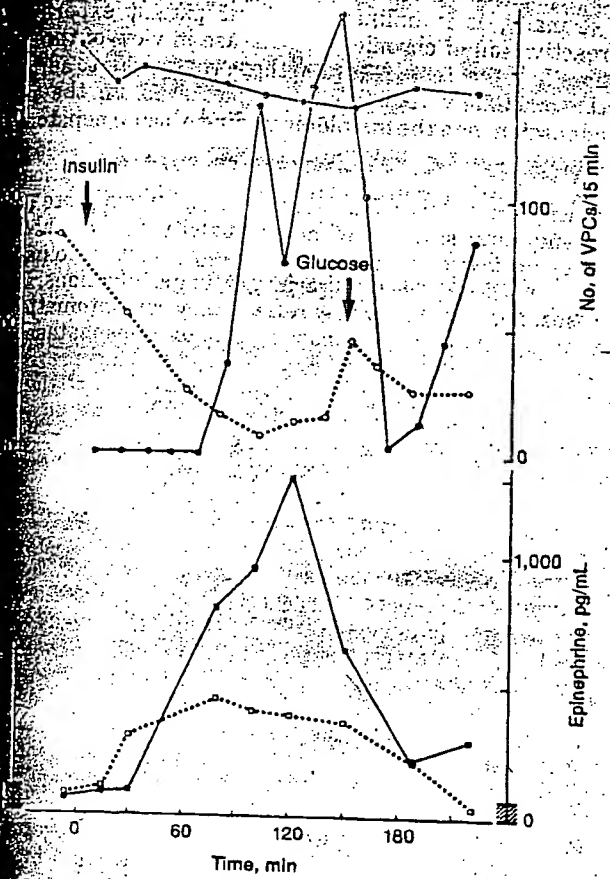

Changes in serum potassium level (solid circles and line at top), blood glucose level (open circles and dotted line), number of ventricular premature contractions (VPCs) per ites (solid circles and line at center), plasma norepinephrine pen squares and dotted line at bottom), and plasma epi- e level (solid squares and line at bottom) during insulin test. Serum potassium level fell from 4.3 to 3.3 mEq/L. As lucose level fell to about 50 mg/dL, VPCs occurred and were ased by glucose administration ("Glucose" section at cen- ntricular premature contractions, however, increased again current fall of blood glucose level. Plasma norepinephrine se before VPCs occurred and began to decrease before attained maximal frequency and did not rise after glucose tration. Plasma epinephrine level did not change for 30 but showed sharp increase at 75 minutes and reached m level at 120 minutes. It fell after glucose administration again as changes in number of VPCs. Normal ranges for lamine levels are indicated as shaded areas in bars at

lood glucose level as compared with that in the awake his possibility might explain the discrepancy be- he blood glucose level and VPCs during sleep.

g the insulin tolerance test, paroxysm of VPCs concomitantly not only with elevations of plasma lamine levels but also with a fall in the serum m level to 3.3 mEq/L. Previous investigators that hypokalemia itself does not seem to produce nias until the serum potassium level falls below /L.[9] A rapid fall in the serum potassium level, may at least contribute to the occurrence of VPCs ction with increased catecholamine levels.

might be a threshold of blood glucose to cause the range of 50 mg/dL. In a study of normal persons, plasma epinephrine levels increased when the blood glucose levels fell to about 30 to 40 mg/dL.[10] In diabetic patients, the level of blood glucose to cause a rise in the level of plasma epinephrine may be set high.

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Fatal Hepatitis Associated With Ketoconazole Therapy

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• A 67-year-old woman receiving ketoconazole, 200 mg daily for two months, had progressive jaundice, anorexia, and malaise develop. She had greatly elevated liver enzyme levels on hospital admission, and she died as a result of rapidly progressive liver failure. Histologic findings at autopsy disclosed acute hepatic necrosis. There was no clinical or serologic evidence of viral hepatitis. It is suggested that ketoconazole therapy was a causal factor in this case of fatal hepatic failure.

(*Arch Intern Med* 1984;144:1069-1070)

Ketoconazole (Nizoral), an orally effective antifungal agent, is known to cause mild hepatitis[1] and transient elevation of liver enzyme levels.[2] Withdrawal of the drug results in normalization of liver enzyme levels in some cases, while in others, liver enzyme levels normalize despite continuation of treatment.[3] The following case, to our knowledge, is the first report of fatal hepatitis associated with ketoconazole therapy.

REPORT OF A CASE

A 67-year-old woman became jaundiced following two weeks of progressive malaise, anorexia, and vague abdominal discomfort.

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EXHIBIT 2

She had no fever. She denied parenteral drug use, receipt of blood products, alcohol intake, or exposure to persons with hepatitis. She had been taking ketoconazole, 200 mg/day, for onychomycosis for two months prior to hospital admission. When she became ill, she discontinued this medication.

She had a history of mild hypertension controlled with hydrochlorothiazide and angina treated with isosorbide dinitrate and nitroglycerin. Since 1975, she had had recurrent urinary tract infections for which she had received multiple courses of both sulfonamides and sulfamethoxazole-trimethoprim; she had been taking sulfamethoxazole-trimethoprim up to two weeks before admission. In 1978, three years prior to the present illness, she had had liver function tests done as part of a routine examination; the bilirubin, SGOT, SGPT, alkaline phosphatase, and lactic dehydrogenase values were normal at that time.

On examination, she was afebrile and jaundiced but had no stigmata of chronic liver disease. There was no rash or lymphadenopathy. Results of cardiorespiratory examination were unremarkable. The abdomen was protuberant with decreased bowel sounds and was slightly tender to deep palpation over the right upper quadrant. The liver and spleen were not palpable, and no ascites was detected.

Initial laboratory values included a WBC count of 12,100/cu mm, with 76% neutrophils, 21% lymphocytes, 2% monocytes, and 1% eosinophils. Results of other laboratory studies disclosed the following values: hemoglobin, 13 g/dL; hematocrit, 38.9%; prothrombin time, 63%; SGOT, 2,300 IU (normal, 9 to 30 IU); SGPT, 1,580 IU (normal, 5 to 35 IU); alkaline phosphatase, 69 units (normal, 9 to 35 units); and total bilirubin, 15 mg/dL (normal, 1 mg/dL), direct, 9 mg/dL.

Shortly after hospital admission, the patient became progressively jaundiced, anorectic, and lethargic. The mononucleosis spot test was negative, as were tests for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis A antibody. The SGOT level rose to 4,080 IU, the SGPT level rose to 1,630 IU, and the bilirubin level rose to 25 mg/dL, while the prothrombin time fell to 29%.

By the ninth hospital day, the patient was encephalopathic and was treated with lactulose, neomycin sulfate, magnesium citrate, and protein restriction. Despite these measures, the patient lapsed into coma. On the 11th hospital day, she had a cardiorespiratory arrest from which she could not be resuscitated.

At autopsy, the liver weighed 900 g and had a wrinkled capsule. Microscopically, there was acute massive hepatic necrosis with bile stasis. The spleen weighed 240 g and showed only mild congestion. There was mild pulmonary edema.

COMMENT

Ketoconazole has been reported to cause only transient elevation of liver enzyme levels or clinically mild hepatitis. We believe our case implicates ketoconazole as a cause of lethal hepatotoxicity. The Food and Drug Administration has since received reports of two additional cases of fatal hepatitis related to ketoconazole administration.[4] However, in each of these two instances, the patients had severe underlying disease that could have caused hepatic failure and death, whereas our patient had been clinically well and had been given ketoconazole only for onychomycosis.

While our patient had been exposed to another potential liver toxin, sulfamethoxazole-trimethoprim,[5] she did not have the fever, rash, or eosinophilia that is usually associated with hepatotoxicity due to sulfonamides.[6] In addition, she had been given sulfamethoxazole-trimethoprim many times over a period of six years without incident.

Although we recognize that some cases of viral hepatitis may mimic drug-induced hepatotoxicity,[7] there is little to support a diagnosis of viral hepatitis in our patient. Hepatitis A and B were excluded by the results of serologic tests. Non-A, non-B hepatitis infection cannot be ruled out, but it is a rare cause of fulminant hepatitis in the elderly. Furthermore, our patient had no history of parenteral exposure, which, at least in older patients, underlies as many as [illegible] the cases of non-A, non-B infection.[8]

Finally, it is unlikely that our patient experienced reactivation of chronic liver disease in view of the normal liver function tests recorded three years prior to admission, the extremely high liver enzyme levels on the day of admission, and the histologic finding of acute hepatocellular necrosis alone at autopsy.

In 1983, investigators from Janssen Pharmaceutica, manufacturers of ketoconazole, attempted to estimate the frequency and severity of hepatotoxicity due to the drug.[9] They reviewed the records of 3,600 patients who had been given ketoconazole for a variety of fungal infections. In these cases, hepatotoxicity was reflected by asymptomatic elevations of serum transaminase or alkaline phosphatase levels. These abnormalities occurred at any time during treatment and often returned to normal despite the fact that ketoconazole therapy was continued. Although the enzyme elevations were not uncommonly seen, they had no value in predicting in which patients symptomatic hepatotoxicity would eventually develop. Thus, periodic screening of transaminase determinations in patients receiving prolonged courses of ketoconazole may serve no clinical purpose.

Their review (through Sept 15, 1982) identified [illegible] symptomatic hepatotoxicity occurring during ketoconazole therapy. Patients became clinically ill after a median of [illegible] weeks of treatment. Two thirds of the patients were older than 50 years of age, and men and women were equally affected. With the exception of our patient who died of massive hepatic necrosis, all others recovered uneventfully once treatment with ketoconazole was discontinued.

In view of the extensive use of ketoconazole and the low incidence of reported toxic reactions,[10] symptomatic hepatotoxicity caused by the drug probably represents an idiosyncratic reaction. Janssen and Symoens[8] have estimated the incidence of such hepatotoxicity to be on the order of one in 12,000. However, that ketoconazole can be potentially hepatotoxic is attested to by our case and by that of Heiberg and Svejgaard.[1] Rechallenge of their patient with the drug caused a recurrence of clinical symptoms, elevated transaminase levels, and abnormal findings on liver biopsy specimen. Unfortunately, since elevated transaminase levels do not necessarily herald symptomatic liver disease, it would appear prudent to advise patients to discontinue ketoconazole and seek medical advice whenever symptoms or signs compatible with hepatitis occur.

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RIES CITED BY BROWN

ean duration of disease (yr)	Dementia
..	3%
8	5%
7	14%
..	9%

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nces in Parkinson's disease. *Dis*

W, Goodell M. Mental symptoms nent with levodopa. *Neurology*

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natural history and dementia of

sease. *Acta Neurol Scand* 1976; 54:

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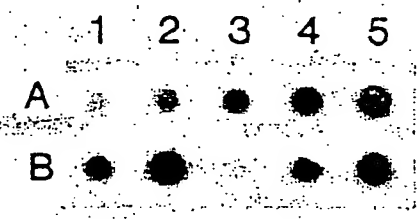
IN THE KIDNEY

(factor VIII:C) is required blood-clotting cascade. A factor VIII:C causes the ia A. The cloning and ished that it is synthesised cell hybridoma, AL7. The ls of factor VIII:C in cases tic sources of this protein. udies have suggested that ung, spleen, and, possibly, n synthesis and storage of ned segment of the human NA isolated from cell lines have confirmed that factor er and shown that it is also

of diverse origin (Hep G2, kidney, MDCK, MDBK, endothelial cells from the al human liver and kidney. III:C mRNA by dot-blot ranslated 4300 base-pair 931 base-pairs of exon 14, –1740 of factor VIII:C e). Of the cells and tissues reparations demonstrated , factor VIII:C mRNA was



Analysis of human kidney and liver for factor VIII:C mRNA.

Total RNA was isolated from normal human liver, kidney, and an embryonic kidney cell line (HEK) that synthesises urokinase.[5] Poly(A)-containing RNA was prepared from the liver and kidney preparations and the samples were analysed by dot-blot hybridisation.[6]

(A) spots 1–5: 0·625, 1·25, 2·5, 5·0, and 10·0 pg of 4300 base-pair genomic DNA fragment, respectively.

(B) spots 1–5: 10 μg of total kidney, poly A^+ kidney, total HEK, total liver, and poly A^+ liver RNA, respectively.

enriched in the poly(A)-containing fraction (figure). The abundance of factor VIII mRNA in these tissues appears similar and represents about 1 in 100 000 of total mRNA molecules. The presence of factor VIII:C mRNA in these tissues has been confirmed by the isolation of cDNAs from both which encode portions of factor VIII:C. Hybridisation of the probe to histological sections of kidney and liver should identify the cell type within each tissue that is responsible for the production of this protein. Immunocytochemical studies have previously suggested that factor VIII:C is present in the endothelial cells of the hepatic sinusoids.[7]

The relative contribution of the kidney to the pool of factor VIII:C remains to be determined. However, the demonstration that it is synthesised by both the kidney and liver should facilitate analysis of its biosynthesis.

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ADRENAL HYPOFUNCTION IN PATIENTS TAKING KETOCONAZOLE

SIR,—Ketoconazole seems to be a useful agent in the management of systemic mycoses[1] and advanced prostatic carcinoma.[2] However, adrenal corticosteroid biosynthesis and the cortisol response to exogenous corticotropin may be acutely suppressed by a single dose of 400 mg of drug for up to 8 h.[3] Features suggesting hypoadrenalism have been reported in one case;[2] and we would like to emphasise the importance of this drug-induced side-effect.

We have studied six patients with advanced prostatic carcinoma taking 1200 mg ketoconazole daily, in equally divided doses. Patients showed significant blunting of 'Synacthen' mediated

cortisol responses 48 h after starting therapy, and thre continued to do so from time to time for up to 6 months aft ketoconazole. 24 h urinary free cortisol fell to abnormally (less than 120 nmol) in two patients; in one this was obser an episode of acute bronchopneumonia, and in th significant hyperpigmentation was noted after 3 month patients with blunted cortisol responses had persistent sy malaise and anorexia.

These provisional data suggest that in any subject tre high-dose ketoconazole, relative corticosteroid defici ensue and replacement treatment should be considered, p in the event of stress.

A full report of these data will be published elsewhe believe that these findings have serious implications whic prescribing this drug should know about.

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1. Heel RC, Brogden RN, Carmine A, Morley PA, Speight TM, Ketoconazole: a review of its therapeutic efficacy in superficial and sys infections. *Drugs* 1982; 23: 1–36.
2. Trachtenberg J, Pont A. Ketoconazole therapy for advanced prostate ca 1984; ii: 433–35.
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CIMETIDINE VERSUS RANITIDINE

SIR,—A potentially important point of clinical-trial des from Dr Gough and his colleagues' report of the (Sept 2 comparison of one-year maintenance treatment with ran cimetidine in duodenal ulceration. A survey of tw published reports of duodenal ulcer maintenance trials w drug did not lead us to expect an important difference i efficacy between the recommended bedtime maintenanc cimetidine (400 mg) and ranitidine (150 mg). Examination and colleagues' report suggests that an inadvertent bias may have contributed to the higher relapse rate four cimetidine group.

Patients were told to take three tablets every night, two container and one from another. These tablets were e active cimetidine 200 mg and one placebo ranitidine or c ranitidine 150 mg and two placebo cimetidine. Compli estimated by counting returned tablets, and patients who more than 40% were excluded from the analysis. Such check on compliance is complicated in this trial by the fac 200 mg tablet of cimetidine produces only a moderate and reduction of overnight gastric acidity[1] and is not an bedtime dose for maintaining ulcer healing. Thus the clin of missing one of the two cimetidine tablets is likely to appr of missing one ranitidine tablet. In the presence of appare compliance, assessed as percentage of tablets returned, ir treatment due to lack of compliance could have occurred o many days in the cimetidine group as in the ranitidir Statistical calculations show that this likelihood could be a factor of two and can only work "against" cimetidine.

While there were fewer relapses in the ranitidine group and second 4-month periods, the trend was reversed in period. One explanation could be that a higher proporti compliant patients relapsed earlier in the study. Thus by period the effect of the compliance bias mentioned abc have been substantially reduced.

It is impossible to judge how important this design bias been clinically. The fact that patients included in the fin could have missed up to 40% (or more) of their tablets allows a potential for such a bias to have affected the res crude year-end relapse rate for the cimetidine group was ju than that found, the difference between the treatment gro not have been significant.

We suggest that this source of bias should be cons planning trials "blinded" by the double-dummy techr have found that over half of a random selection of publish which this technique was used were potentially subje weakness, which is usually easy to avoid. The point is

cortisol responses 48 h after starting therapy, and three of these continued to do so from time to time for up to 6 months after starting ketoconazole. 24 h urinary free cortisol fell to abnormally low levels (less than 120 nmol) in two patients; in one this was observed during an episode of acute bronchopneumonia, and in the second significant hyperpigmentation was noted after 3 months. All five patients with blunted cortisol responses had persistent symptoms of malaise and anorexia.

These provisional data suggest that in any subject treated with high-dose ketoconazole, relative corticosteroid deficiency may ensue and replacement treatment should be considered, particularly in the event of stress.

A full report of these data will be published elsewhere but we believe that these findings have serious implications which doctors prescribing this drug should know about.

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3. Pont A, Williams PL, Loose DS. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; 97: 370–72.

CIMETIDINE VERSUS RANITIDINE

SIR,—A potentially important point of clinical-trial design arises from Dr Gough and his colleagues' report of the (Sept 22, p 659) comparison of one-year maintenance treatment with ranitidine or cimetidine in duodenal ulceration. A survey of twenty-five published reports of duodenal ulcer maintenance trials with either drug did not lead us to expect an important difference in clinical efficacy between the recommended bedtime maintenance doses of cimetidine (400 mg) and ranitidine (150 mg). Examination of Gough and colleagues' report suggests that an inadvertent bias in design may have contributed to the higher relapse rate found in the cimetidine group.

Patients were told to take three tablets every night, two from one container and one from another. These tablets were either two active cimetidine 200 mg and one placebo ranitidine or one active ranitidine 150 mg and two placebo cimetidine. Compliance was estimated by counting returned tablets, and patients who returned more than 40% were excluded from the analysis. Such a routine check on compliance is complicated in this trial by the fact that one 200 mg tablet of cimetidine produces only a moderate and transient reduction of overnight gastric acidity[1] and is not an adequate bedtime dose for maintaining ulcer healing. Thus the clinical effect of missing one of the two cimetidine tablets is likely to approach that of missing one ranitidine tablet. In the presence of apparently equal compliance, assessed as percentage of tablets returned, inadequate treatment due to lack of compliance could have occurred on twice as many days in the cimetidine group as in the ranitidine group. Statistical calculations show that this likelihood could be more than a factor of two and can only work "against" cimetidine.

While there were fewer relapses in the ranitidine group in the first and second 4-month periods, the trend was reversed in the third period. One explanation could be that a higher proportion of less compliant patients relapsed earlier in the study. Thus by the third period the effect of the compliance bias mentioned above would have been substantially reduced.

It is impossible to judge how important this design bias may have been clinically. The fact that patients included in the final analysis could have missed up to 40% (or more) of their tablets certainly allows a potential for such a bias to have affected the results. If the crude year-end relapse rate for the cimetidine group was just 4% less than that found, the difference between the treatment groups would not have been significant.

We suggest that this source of bias should be considered in planning trials "blinded" by the double-dummy technique. We have found that over half of a random selection of published trials in which this technique was used were potentially subject to this weakness, which is usually easy to avoid. The point is especially important in a long-term trial where compliance with recommended treatment must always be a concern.

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1. Longstreth GF, Go VLW, Malagelada J-R. Cimetidine suppression of nocturnal gastric secretion in active duodenal ulcer. *N Engl J Med* 1976; 294: 801–04.

SIR,—Dr Gough and colleagues' study comparing the efficacy of ranitidine with cimetidine in preventing relapse of duodenal ulcer needs to be viewed from a clinical perspective. Considerable energy was required to organise a year-long, demanding study of 484 patients recruited from fifty-one centres but the endoscopic method of evaluating these two drugs was geared more to official acceptance for marketing than to evaluation of clinical efficacy. Maintenance therapy with both drugs works well symptomatically.

With the proliferation of effective new drugs for treating duodenal ulcer, there will doubtless be many more such papers comparing the efficacy of one drug with another in preventing duodenal-ulcer relapse. Has not the time come for us to evaluate these drugs in the real world of accepted clinical practice, rather than to follow slavishly the "gold standard" of endoscopic perfection required for acceptance by the US Food and Drug Administration?

If a patient is feeling well and has experienced no ulcer complications, who cares whether there is, or is not, "a break in the continuity of the [duodenal] mucosa with exudate"[1] by endoscopy? Do we as clinicians so mistrust our clinical evaluations of duodenal ulcer patients treated with effective drugs that we must order endoscopies repeatedly until we have proved the duodenal bulb to be cosmetically acceptable? Must we, to prove remission, do endoscopy on a patient who has been symptom-free for a year while on a maintenance dose of an effective drug? Of course not. Such endoscopic excesses are contrary to the recommendations of three major gastroenterological associations: "Endoscopy has no role in the usual follow-up of asymptomatic and uncomplicated duodenal ulcer."[1]

Boyd et al[2] have shown that it does not matter whether a duodenal ulcer is present at endoscopy if the patient is on ranitidine or cimetidine maintenance therapy because such ulcers are rarely symptomatic and even less likely to give rise to complications. This is not true for asymptomatic duodenal ulcers by endoscopy in patients not on maintenance therapy. Such cases are more likely to become symptomatic and complicated.[2]

Asymptomatic ulcers detected by endoscopy heal spontaneously just as often whether or not maintenance therapy with an H_2 inhibitor is being given.[2] Duodenal ulcers are spontaneously remittent and are not permanently cured by drugs. As physicians, our realistic objective should be to minimise the disability of duodenal ulcer by relieving symptoms and by reducing complications.

What one should look for in a maintenance drug for duodenal ulcer is clinical efficacy and long-term safety. The ideal drug for maintenance therapy would be one that keeps patients symptom-free at the lowest potency dosage, causing the least disturbance of normal gastric function.

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1. The role of endoscopy in the management of patients with duodenal ulcer; Guidelines for clinical application. American Society for Gastrointestinal Endoscopy/American Gastroenterological Association/American College of Gastroenterology; revised January, 1983.
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SIR,—Dr Gough and colleagues conclude that ranitidine is significantly better than cimetidine in preventing duodenal ulcer relapse. However, they ignore the difference in alcohol consumption between the two treatment groups. We suggest that this difference may have biased the results in favour of ranitidine.

Original Investigations

High-Dose Ketoconazole Therapy and Adrenal and Testicular Function in Humans

Allan Pont, MD; John R. Graybill, MD; Philip C. Craven, MD; John N. Galgiani, MD; William E. Dismukes, MD; Richard E. Reitz, MD; David A. Stevens, MD

• **Ketoconazole, an oral antifungal, when given in conventional doses, transiently blocks testosterone synthesis and adrenal response to corticotropin. Higher therapeutic doses (ie, 800 to 1,200 mg/day), even once daily, caused more prolonged blockade. In some men, the serum testosterone concentrations were always subnormal. Bound and free testosterone values were equally diminished. Oligospermia and azospermia after prolonged therapy were noted. Impotence and decreased libido were found. Gynecomastia appeared more common than with lower doses. Depressed response to corticotropin was pronounced. Urine cortisol excretion was depressed. The blockade appeared related to the serum ketoconazole concentration. Instances of normal hormone levels or responsiveness were associated with low ketoconazole concentrations. The hormonal effects were generally unrelated to duration of therapy, although there may have been partial reversal with continued therapy. These effects appeared reversible with discontinuation of therapy. Patients receiving ketoconazole should be considered potentially unable to mount an adrenal stress response and may require testosterone supplementation.**

(*Arch Intern Med* 1984;144:2150-2153)

Ketoconazole is an oral antifungal agent with reported efficacy against a variety of pathogenic fungi in man.[1] The development of gynecomastia in some patients taking the drug[2,3] prompted study of the effect of ketoconazole on steroid secretion. Previous reports showed that doses commonly used (and licensed in the United States) for treatment of fungal disease (200 to 400 mg/day) transiently block testosterone synthesis[4] and can blunt the corticotropin response to corticotropin.[5]

Some patients with progressive fungal disease are currently receiving high dosages of ketoconazole (≥800 mg/day), many as participants in ongoing studies conducted by the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group.[6] We have studied testicular and adrenal function in some of these patients. Our results, some of which have been presented in preliminary form, show, to our knowledge for the first time, that these high doses of ketoconazole can produce impotence, azospermia, and considerable diminution of adrenal responsiveness to cortisol secretion.

PATIENTS AND METHODS

Blood, urine, and semen samples were collected from 24 patients at cooperating centers. Many of these patients were enrolled in the multicenter NIH study.[6] All patients in this study were receiving ketoconazole only once daily. Patients were studied with as many of the tests described as logistically possible under multicenter study conditions; in all the data (eg, hormone and drug determinations) to be subsequently given, the denominator number forms the subset of patients who could be studied in a particular test is indicated. The subsets were determined by logistic considerations, and not queries regarding symptoms or results of other tests. Informed consent was obtained from all subjects under guidelines of the research review committee of each of the collaborating centers. Serum and urine samples were shipped frozen to one laboratory for processing. Quantitation of ejaculate sperm was done at the site of collection. We reiterate herein that specimens samples were obtained without relation to whether or not a history of sexual dysfunction had been obtained or to results of other studies. Serum ketoconazole concentration determinations in these patients were performed as part of routine monitoring in the multicenter study, and always without knowledge of the results of the endocrinologic studies. Ketoconazole concentrations were determined as described previously.[9]

Twenty-four patients were examined for gynecomastia. Mammograms were not done. These patients were questioned as to whether impotence or decreased libido had occurred since they started taking the drug.

Response to corticotropin was assessed by the rapid intrave-

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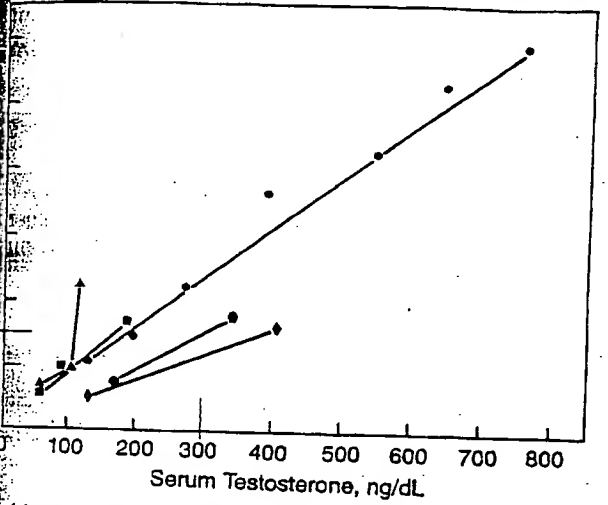
—Lowered Sperm Counts in Patients Receiving High-Dose Ketoconazole Therapy

Ketoconazole, mg/Day	Duration of Therapy, mo	Sperm Count, No./mL
800	12	14×10^6
800	10	30×10^6
800	4 (10)	18×10^6
800	4 (10)	45×10^6
800	8 (9)	0
1,200	5 (12)	0

me patients had been receiving smaller doses before the dose shown; tal duration of ketoconazole therapy is given in parentheses.



ct of ketoconazole on total and free testosterone concentra- Serum total testosterone and unbound (free) testosterone entrations were determined in five patients before and after or 1,200-mg dose of ketoconazole. Each symbol represents es from one patient. Each patient's determinations were done ours after his last ketoconazole dose, and then every four hours east two determinations per patient).

ction of 250 μg of cosyntropin (Cortrosyn); blood for cortisol rmination was drawn before and 60 minutes after the infusion. nty-four–hour urinary free cortisol concentration was mea- d in three patients before starting ketoconazole therapy and initial administration of an 800-mg dose.

rum and urine cortisol[10] and testosterone[11] concentration were sured by radioimmunoassay. The unbound testosterone con- ration was determined by a dialysis technique derived from of Forest et al.[12] Quantitations of ejaculate sperm were done by linical laboratories with counting chambers. The normal value these methods for 24-hour urine cortisol was 20 to 90 μg/day; m testosterone concentration, 300 to 1,100 ng/dL; and sperm t, more than 20 to more than 50 million/mL. A normal cortisol nse to corticotropin is generally accepted as a value 60 es after injection that is at least 7 μg/dL greater than the value, and a peak cortisol value greater than 18 μg/dL.[13]

RESULTS

Gonad Function

erm Counts.—Six of nine patients studied had sperm considered below normal for the laboratory perform- e test; four counts were below the lowest standard by any laboratory (Table 1). Two patients were azo- ic. Ketoconazole therapy was discontinued in one t (No. 6) when azospermia was noted. Three weeks his count was 81,000/mL. Three months later, it was illion/mL; six months later, 26 million/mL; and nine s later, 20 million/mL. Becuase of the recurrence of his coccidioidal disease, therapy was then reinstituted at 800 mg/day. Seven months later, his sperm count was again zero. With this exception, sperm counts had not been done on any of these patients before initiation of their courses of ketoconazole therapy. Another patient (No. 1) was studied after an additional 2½ months of therapy followed by six months without therapy. At the latter time, his sperm count was normal (186 million/mL).

All of the patients with decreased counts had been receiving high dosages (≥800 mg/day) of ketoconazole for more than four months. Of the three patients with normal sperm counts, two had been receiving their present high dose for less than three months. The other had low serum ketoconazole concentrations, presumably because of poor absorption, although altered disposition could not be ruled out. Studies 2, 4, 6, and 8 hours after a 1,200-mg dose showed this patient's peak serum concentration was 2.90 mg/L two hours after the dose. This concentration is essentially the same as the mean peak serum concentration in patients receiving one sixth that dose,[9] while in a report from this multicenter study,[14] the mean (±SE) peak serum concentration in seven patients receiving 1,200 mg, which occurred four hours after the dose, was 14.3 ± 3.8 mg/L; and the mean serum concentration at two hours in nine patients was 8.0 ± 1.3 mg/L.

Other Signs and Symptoms.—Five of 24 patients studied had easily detectable gynecomastia during therapy that had not been noted before treatment. This incidence is higher than that reported[2,5] with lower ketoconazole doses. Five of 24 patients reported impotence, and an additional three of 24 noted decreased libido that reportedly had developed after initiation of ketoconazole therapy. Specific physiologic tests for impotence were not done.

Testosterone Levels.—Sixty-five determinations were done. Twenty-five serum testosterone concentrations were determined after an 800-mg dose. The concentration was below 300 ng/dL in six of eight patients four hours after the dose, in seven of seven patients at eight hours, and in three of ten patients 24 hours after the dose. The latter three had testosterone values of 56, 20, and 187 ng/dL at that time.

Serum testosterone concentrations were determined in six patients 24 hours after a 1,200-mg dose. In three, the concentration was below 300 ng/dL, and all three had even lower values four and eight hours after ketoconazole administration compared with their 24-hour value. We presumed that such patients would never have normal testosterone concentrations while receiving this dose once daily. This was corroborated by an additional 12 serum samples obtained from patients two to 20 hours after 1,200 mg of ketoconazole, all of which had less than 300 ng/dL of testosterone. Of the three patients who had a normal testosterone concentration 24 hours after a 1,200-mg dose, serum ketoconazole concentrations, available in two, were extremely low (≤0.39 mg/L 24 hours after the dose in both).

The duration of ketoconazole therapy in the patients with testosterone studies ranged from one day to 18 months. There was no apparent correlation of duration of therapy and testosterone concentration, with the exception of the testosterone concentrations 24 hours after an 800-mg dose. The three patients receiving 800 mg with testosterone levels below 300 ng/dL 24 hours after the dose had been receiving ketoconazole for up to two weeks (range, one day to two weeks), whereas the seven with normal testosterone concentrations had been receiving ketoconazole for four months or longer (range, four to 18 months).

Eight of the male patients whose testosterone concentrations were determined while receiving 800 and/or 1,200 mg of ketoconazole daily were also studied while not receiving

Table 2.—Effect of High-Dose Ketoconazole Therapy on Cortisol Response to Corticotropin*

No. of Studies	Ketoconazole, mg	Serum Cortisol, µg/dL (Mean±SD)			
		Before Injection†	60 min After Injection†	Difference†	F<18‡
16	0	15.1±8	35.7±8	20.5±9	0
14	800	12.1±6	17.2±7	6.0±4.6	6
11	1,200	9.6±4.9	14.8±11.4	5.3±7.8	7

*Cosyntropin (Cortrosyn), 250 µg, was given intravenously at least 36 hours after last dose of ketoconazole (0-mg dose group) or two to eight hours after 800- or 1,200-mg dose.

†By two-tailed Student's *t* test, serum cortisol concentration before injection was significantly ($P<.03$) different for the 0-mg group *v* 1,200-mg group, and concentration at 60 minutes for the 0-mg group *v* 800- and 1,200-mg groups ($P<.001$ for both); the mean rise in serum cortisol concentration also significantly different between the 0-mg group and the 800- or 1,200-mg groups ($P<.001$ for both).

‡By Fisher's exact test, for peak serum cortisol concentrations less than 18 µg/dL (F<18) criterion, 0-mg group was significantly different from the 800- 1,200-mg groups ($P=.003$ and $P=.005$, respectively).

§By Fisher's exact test, for the rise in serum cortisol concentration less than 7 µg/dL (ΔF<7) criterion, the 0-mg group was significantly different from the and 1,200-mg groups ($P=.003$ for each).

ketoconazole therapy at the same times of day. Six were studied before therapy, and two after discontinuation of therapy, for a total of 22 samples. All 22 testosterone values were normal.

Ketoconazole induced a parallel diminution in both total and unbound testosterone concentrations in five patients tested before and after 800- or 1,200-mg doses (Figure). Four hours after the dose, the mean (±SD) total testosterone level was 37%±14% of baseline and the free testosterone level was 35%±15% of baseline.

Adrenal Function

Corticotropin Response.—The effect of high-dose ketoconazole on the cortisol response to corticotropin is shown in Table 2. All 20 patients studied had normal test results before initiation of therapy or 36 hours after discontinuing therapy. Two to eight hours after an 800- or 1,200-mg dose, however, there was a sharp diminution of cortisol response in most patients. Corticotropin increased serum cortisol concentration less than 7 µg/dL in ten of 14 studies in the 800-mg group and nine of 11 in the 1,200-mg group. Ketoconazole pharmacokinetic data were available in one of the two patients with cortisol increases of more than 7 µg/dL in the latter group, and he also appeared to have altered pharmacokinetics. In two separate studies after an 800-mg dose, his peak serum concentrations were 1.15 and 2.15 mg/L; in contrast, in 34 patients from this multicenter study studied after an 800-mg dose,[14] the peak serum concentration was 9.7±0.8 mg/L. Although the baseline cortisol concentration was in the normal range in the 1,200-mg group, even this value was significantly ($P<.03$) lower than that of the patient group studied when not receiving the drug.

The duration of ketoconazole therapy in the patients with corticotropin studies was less than one week to 18 months. There was no correlation apparent between duration of ketoconazole therapy and adrenal responsiveness to corticotropin.

Urinary Cortisol Concentration.—An 800-mg dose of ketoconazole reduced urinary free cortisol values by approximately 50% in the patients tested (65 to 33 µg/day, 36 to 13 µg/day, and 176 to 87 µg/day).

Signs and Symptoms.—Monitoring of the 111 patients in this study did not disclose symptoms, signs, or other laboratory findings suggestive of hypoadrenalism, eg, there was no evidence of hypotension or pigment changes, and serum electrolyte values were unaltered by ketoconazole therapy.

COMMENT

It had been previously reported that currently licensed dosages of ketoconazole (200 to 400 mg/day) could block testosterone synthesis.[4] Except for three[3] and four[5] case gynecomastia reported elsewhere, however, end-organ fects of diminished testosterone production had not b confirmed. We thought that the lack of reports of deve ment of impotence or a reduction in sperm count could b be explained by the temporal nature of the testosteron synthesis blockade.[4] That is, a single 200- and 400-mg d of ketoconazole reduces testosterone levels for only tw 12 hours, allowing patients to have normal androgen le for most of the day.

The patients in this report had disseminated or prog sive deep mycoses (principally coccidioidomycosis) were receiving high doses of the drug in experim protocols. The duration of depression of serum testoster was longer than previously reported[4] with lower do About one third of the patients taking 800 mg/day had testosterone levels throughout the day, ie, their se testosterone concentrations appeared never to come the normal range during ketoconazole therapy. This in dence appeared to be even higher after 1,200 mg of ketoc azole daily. We cannot be certain why low testostero levels were not seen in every patient. Possible explanation include diminished gastrointestinal absorption of the dru accelerated drug metabolism, individual resistance to t steroid-lowering effects, and/or increased counterregul tory mechanisms. The data presented herein suggest th the steroid-lowering potential of ketoconazole depen most on the serum drug concentrations that are prese and thus the lack of blockade would be less likely explain by the latter two postulates. That is, patients who do have high serum ketoconazole concentrations throughou the day may not have consistently low testosterone levels depressed adrenal responses to corticotropin. More da are needed, however. Earlier studies do support the co cept that the likely explanation for whether or not ster blockade occurs lies in the serum ketoconazole concentra tion. Studies with rats showed depressed in vitro testoste one synthesis in the presence of ketoconazole but norm synthesis in vitro by Leydig's cells from rat testes excise after ketoconazole administration and cultured in the a sence of added ketoconazole.[4] Studies of isolated dog test indicated block of testosterone synthesis was present du ing but not after ketoconazole perfusion.[15] Finally, th earlier human studies[4] indicated a temporally inverse re tionship between serum ketoconazole and testostero concentrations.

Ninety-eight percent of circulating testosterone is boun to sex-hormone-binding globulin, and 2% is free.[16] T unbound fraction is considered responsible for hormon action.[17] We had considered the possibility that end-org

...might be preserved if ketoconazole could displace ...rone from its binding globulin, thus increasing the ...tion. In vitro studies suggest displacement of ...rone from sex hormone–binding globulin by keto-...ole.[17] We did not find supportive evidence, however, ...this was important in vivo. In the five patients studied, ...el diminution occurred in both total and free hor-...concentration. Others have previously shown that ...nazole induces a reduction in serum and salivary ...terone concentrations.[18] The salivary testosterone ...tration is considered to be a good index of the ...nd fraction of the hormone.[19]

...ability of ketoconazole to lower testosterone produc-...sulted in end-organ effects in our patients who were ...ing high doses of the drug. Six of nine had reduced ...m counts, and two were azospermic. Decreased libido ...impotence were common. The sperm count of one pa-...m whom the drug therapy could be discontinued was ...ing toward normal. Then ketoconazole administra-...was reinstituted, and he again became azospermic. ...other patient's sperm count became normal while not ...ng therapy. We had not assessed erectile function in ...patients before commencement of therapy; thus, we ...be entirely certain of a cause-and-effect relationship ...en ketoconazole and erectile dysfunction. This was ...common than expected, however, and our patients ...decreased libido after starting the drug therapy. The ...plaints of impotence elicited should be verified in future ...es with physiologic tests of erectile function. The ...ved sperm count in two patients well enough to permit ...tion of drug therapy, and the recurrence of azospermia ...when drug therapy was reinstituted, very strongly ...sts a cause-and-effect relationship. The course of ...sperm counts while not receiving the drug also implies ...the gonadal effects are reversible.

...showed that high doses of the drug block cortisol ...tion. The cortisol response to corticotropin was ...d, and the daily urine cortisol excretion was reduced ...Preliminary data indicate that serum cortisol values ...de greatly reduced throughout the day in occasional ...nts taking high doses of ketoconazole.[7] As yet, how-...one preliminary report of a case[20] represents the only ...nce of a patient receiving ketoconazole and showing signs or symptoms suggestive of hypoadrenalism. The general failure of ketoconazole to induce hypoadrenal symptomatology despite its potent in vitro and in vivo glucocorticoid-lowering effect[5] requires further investigation. It is possible that ketoconazole has glucocorticoid agonist properties or that the drug affects the binding of glucocorticoids to their binding globulin. A lack of effect on such binding has been reported in in vitro studies.[15] In the interim, however, until this phenomenon is better understood, we suggest that patients taking high doses of ketoconazole be considered at risk for hypoadrenal crisis.

Given the generation time necessary for production of spermatozoa, the correlation found between duration of therapy and oligospermia is easily understood. Because the number of patients failing to show either hormone suppression at the doses studied was small, the circumstances were not ideal for attempting correlations between suppression and duration of therapy. It was therefore of interest to note the correlation found between length of therapy with 800 mg of ketoconazole daily and *lack* of prolonged circadian depression of testosterone. It is possible that this could be explained by loss of Leydig's cell sensitivity to ketoconazole effect with time, but it seems more likely that this relates to an earlier preliminary observation[8] in two patients that ketoconazole serum concentrations decline with prolonged 800-mg daily therapy. Another patient studied in similar fashion, however, did not show this decline.[21]

This report shows that high doses of ketoconazole can severely diminish testosterone and cortisol secretion. Functional hypogonadism, which is probably reversible, is seen in some patients. The clinical use of high doses of the drug will depend on the efficacy of ketoconazole in treating serious fungal disease balanced against drug-related side effects. Currently licensed dosages of ketoconazole (200 to 400 mg daily) diminish steroid secretion, but hormone-related side effects are rare. As previously suggested,[3,5,7] the ability of ketoconazole to block testosterone synthesis might prove advantageous. Preliminary data indicate success in treating advanced prostate carcinoma.[22]

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